FACT SHEET
Healthcare Provider

Sickle Cell Disease

Description:
Hemoglobinopathies are a group of autosomal recessive disorders characterized by synthesis of abnormal hemoglobin molecules (e.g., S, E, C) or decreased synthesis of alpha or beta globin chains.

Sickle cell disease (SCD) is a collective term for a group of genetic disorders characterized by the predominance of hemoglobin S (Hb S). These disorders include sickle cell anemia (SS), the sickle beta thalassemia syndromes ($S\beta^+$ or $S\beta^0$), and hemoglobinopathies in which Hb S is present in combination with another variant hemoglobin. The most common examples include hemoglobin SC disease, hemoglobin SD disease, and hemoglobin SE disease.

There are two main pathophysiologic features of sickle cell disorders: chronic hemolytic anemia and vasoocclusion. Hemolytic anemia may be related to repeat cycles of sickling and unsickling, which interact to produce irreversible red cell membrane changes, red cell dehydration, and erythrocyte destruction. Tissue injury is usually produced by ischemia and infarction. The organs at greatest risk are those with venous sinuses where blood flow is slow and oxygen tension and pH are low (e.g., spleen and bone marrow) or those with a limited terminal arterial blood supply (e.g., eye, head of the femur and humerus). No tissue or organ is spared from this injury. Symptoms of the hypoxic injury may be either acute (e.g., painful events, acute chest syndrome) or insidious in onset (e.g., aseptic necrosis of the hips, sickle cell retinopathy). The effects of acute and chronic tissue injury may ultimately result in failure of organs like the kidney, particularly as the patient ages.

Symptoms:
The clinical course of sickle cell anemia does not follow a single pattern; some patients have mild symptoms, while others have very severe symptoms. Symptoms may be less severe or different in children who have inherited a sickle cell gene from one parent and a different abnormal hemoglobin gene from the other. Complications may include, but are not limited to, the following:

- **Hand-foot syndrome:** Dactylitis is the most common first sign of sickle cell disease in some infants. Signs include painful swelling of the hands and feet.
- **Infection:** Children with sickle cell disease are at increased risk for certain bacterial infections. It is important to watch for fevers of 101 degrees Fahrenheit (38.33 degrees Celsius) or higher, which could signal an infection. **A clinician should see children with sickle cell disease and fever immediately.**
- **Splenic sequestration crises:** Sickled red blood cells become trapped in the spleen, leading to fewer cells in the general circulation. Any enlargement of the spleen is of concern and must be watched for changes. Early signs include oral pallor, lethargy, an enlarged spleen, and pain in the abdomen.
- **Painful crises:** These may occur in any part of a child's body. Body cooling, fever, or dehydration may be triggers. Pain may last a few hours or up to 2 weeks or even longer.
- **Acute chest syndrome:** ACS is a result of sickling in the lungs and is associated with a new infiltrate on chest x-ray. Symptoms of ACS include cough, chest pain, fever, sputum production, dyspnea, or hypoxia. Infection is the most common identified cause, but pain is a frequent preceding event. Symptoms require emergency evaluation and treatment. This condition develops more often in young children but is usually more severe in adults.
- **Aplastic crisis:** Aplastic sickle cell crises occur when the bone marrow temporarily shuts down. The causative agent is usually human parvovirus B19. Because of the shortened red cell survival, marrow shutdown leads to profound anemia over a period of a few days. Signs include paleness and fatigue.

Parental education is very important so that they learn to recognize this condition early and seek medical treatment.

- **Stroke:** Decreased blood flow to the brain can occur from the sickle-shaped cells blocking small blood vessels. This may lead to a stroke. Signs may include headache, seizures, weakness of the arms and legs, speech problems, a facial droop, and loss of consciousness. Other possible complications include; leg ulcers, bone or joint damage, gallstones, kidney damage, priapism**,** eye damage, and delayed growth.

Incidence in General Population:
Sickle cell disease affects millions worldwide. It is particularly common among people whose ancestors come from sub-Saharan Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy. In the Unites States, it affects around 72,000 people, most of whose ancestors come from Africa. The disease occurs in about 1 in every 350 African-American births and 1 in every 1,000 to 1,400 Hispanic-American births. About 2 million Americans, or 1 in 12 African Americans, carry the sickle cell trait.

Diagnosis:
Screening for sickle cell disease is done using dried-blood-spot screening tests. All first filter paper samples are screened for hemoglobinopathies using Isoelectric focusing (IEF). Various hemoglobin patterns occur. If an abnormality is detected, the sample is reanalyzed using high performance liquid chromatography (HPLC). A fresh sample is requested for confirmation of critical lab results. Family studies are needed to differentiate between homozygous sickle cell anemia and sickle beta ^{0} thalassemia.

Monitoring:
Health care monitoring and maintenance with appropriate immunizations is imperative to the health of the infant with sickle cell disease. Newborns should be referred to a Pediatric Comprehensive Sickle Cell Center for ongoing disease management, parent education, and genetic counseling after a diagnosis of sickle cell disease has been confirmed. It is important that the primary care provider and the Comprehensive Sickle Cell Center develop an ongoing, collaborative relationship in caring for these patients. Please see Table 1 for suggested routine clinical laboratory evaluations.

Table 1. Suggested Routine Clinical Laboratory Evaluations

Tests	Age	Frequency
CBC with WBC differential	3 mo – 24 mo	every 3 mo
Reticulocyte count	>24mo	every 6 mo
Percent Hb F	12 mo – 24 mo >24 mo	annually every 12 mo
Renal function (creatinine, BUN, urinalysis)	≥ 12 mo	annually
Hepatobiliary function (ALT, fractionated bilirubin)	≥ 12 mo	annually
Pulmonary function (transcutaneous O_2 saturation)	≥ 12 mo	annually

Transcranial Doppler ultrasonography (TCD), magnetic resonance imaging (MRI) with or without angiography, and neuropsychometric (NPM) studies have been used extensively to evaluate children with SCD. An abnormally high blood flow velocity by TCD in the middle cerebral or internal carotid arteries is associated with an increased risk of stroke; however, blood flow results should be interpreted cautiously because they are dependent on the technique employed. TCD screening of children with homozygous sickle cell disease (SS) is recommended to start at 2 years of age and continue annually until 16 years of age if TCD is normal and every 4 months if TCD is marginal. Abnormal results should be repeated within 2 to 4 weeks. Children with SCD who have "silent" cerebral infarcts detected by MRI have a higher rate of abnormal NPM studies and a higher risk for overt strokes. Stroke prevention strategies based on

abnormal MRI results have not been tested, but children with abnormal MRI or NPM studies could be evaluated more frequently and carefully and considered for therapeutic measures.

Pulmonary function tests (PFT) should be done regularly in those with history of recurrent acute chest episodes or low oxygen saturation. Lung function declines with age, so it is important to identify those who need close monitoring and treatment.

Treatment:
Any sign of illness in an infant with sickle cell disease is a potential medical emergency. The most important intervention in the routine management of children with SCD is penicillin prophylaxis to prevent pneumococcal infection. The National Institutes of Health clinical guidelines for management of sickle cell disease state, "Penicillin prophylaxis should begin by 2 months of age for infants with suspected sickle cell anemia, whether or not the definitive diagnosis has been established." Antibiotic therapy should continue until at least 5 years of age. Normal dosage for an infant is 125 mg of penicillin twice a day until 3 years of age, when dosage is increased to 250 mg twice a day.
Prescription pain medication may be indicated during a vasoocclusive event.

Hydroxyurea, a cancer medication, has been shown to reduce complications in sickle cell anemia by reducing the frequency of painful crises and episodes of acute chest syndrome. Currently, researchers are studying a number of new drug treatments for reducing complications of the disease.

Additional treatments may include:
- Partial exchange transfusion for acute chest syndrome.
- Transfusions or surgery for neurological events, such as strokes.
- Dialysis or kidney transplant for kidney disease.
- Irrigation or surgery for priapism.
- Surgery for eye problems.
- Hip replacement for avascular necrosis of the hip (death of the joint).
- Gallbladder removal (if there is significant gallstone disease).
- Wound care, zinc oxide, or surgery for leg ulcers.

Bone marrow transplants can be curative; however, this therapy is indicated in only a minority of patients due to the high risk of the procedure and difficulty in finding suitable donors.

Immunizations:
In addition to routine immunizations, children with SCD require additional immunizations. The recent introduction of the pneumococcal conjugated vaccine (PCV) is important for those with SCD. Prevnar (Wyeth-Lederle), the 7-valent PCV (PCV7) licensed in the United States, covers pneumococcal serotypes 4, 9V, 14, 19F, 23F, 18C, and 6B, and has possible cross-reactivity with serotypes 6A, 9A, 9L, 18B, and 18F. Together these serotypes account for 87% of bacteremia and 83% of meningitis due to pneumococcus in the United States. The American Academy of Pediatrics (AAP) recommends Prevnar for children with SCD up to 59 months of age. Please see Table 2 for the recommended schedule of pneumococcal immunizations for previously unvaccinated children with SCD. Please see Table 2 for the recommended schedule of pneumococcal immunizations for previously unvaccinated children with SCD.

Table 2. Recommended Schedule of Pneumococcal Immunizations for Previously Unvaccinated Children With Sickle Cell Disease

Product Type	Age at 1st dose	Primary Series	Additional Doses
PCV7 (Prevnar)	2-6 mo 7-11 mo ≥ 12 mo	3 doses 6-8 wk apart 2 doses 6-8 wk apart 2 doses 6-8 wk apart	1 dose at 12 to <16 mo 1 dose at 12 to <16 mo --
PPV23 (Pneumovax)	≥ 24 mo	1 dose at least 6-8 wk after last PCV7 dose	1 dose 3-5 yr after first PPV23 dose

Growth and Development:
Delayed growth and puberty in children is dependant upon the severity of anemia.

November 2005